Amendments to the Drawings

The attached sheet of drawings includes changes to Figures 3A, 3B, and 3C. This sheet, which includes Figures 3A, 3B, and 3C, replaces the original sheet including Figures 3A 3B, and 3C. In the Replacement Sheet, references to SEQ ID NOS are deleted.

Attachments: Replacement Sheet
Annotated Sheet Showing Changes

REMARKS

Claims 31, 34-42, 45-59, and 67-96 are pending, of which claims 31, 39, 40 and 42 are currently amended. Claims 34-35, 45-59, and 67-96 are withdrawn as being directed to a non-elected species or group. Claims 32-33 and 43-44 are cancelled. Claims 31, 39, 40 and 42 are amended for clarity and to further distinguish the invention from the cited prior art. As no new matter is introduced, entry of the amendments at this time is warranted.

In the Office Action, the declaration is noted to be defective for missing the residence and city information. Accordingly, a new declaration is submitted herewith for substitution for the one that is already of record. The new declaration includes all address information for the inventors.

The Examiner also notes that a certified copy of the priority document is not filed. Accordingly, a certified copy of the priority document, Israeli Application No. 00142118, is herewith submitted.

In response to the Examiner's comments on the sequences on page 24 of the application, a substitute Sequence Listing is submitted. The relevant portion on page 24 of the specification is amended to reflect this change.

The Examiner objects to the specification for not providing all the details of Figure 4. However, Figure 4 is described at page 25 of the specification, which identifies B, H, and Xa in Figure 4 as BamHI restriction enzyme site, HindIII restriction enzyme site, and Xa as a factor Xa cleavage site, respectively (see p. 25, lines 5-6). The specification also describes Linker A as "a simple flexible linker encoding six amino acids: Gly Gly Ser Gly Gly Ser" and Linker B as harboring "an MMP9-specific cleavage sequence" (p. 25, lines 3-4). Therefore, this objection should be withdrawn.

Figures 3A-3C in the drawings are objected to for the reasons stated on page 3 of the Office Action. In response, Figures 3A-3C are amended and a replacement sheet of drawings including Figures 3A-3C is submitted herewith.

Claims 43-44 are objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form. Claims 43-44 are cancelled, and this objection is overcome.

Claim Rejections -- 35 U.S.C. § 112

Claims 31-32, 36-38, and 40-44 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons stated on pages 5-7 of the Office Action. In response, claim 31 is amended to recite at least one

natriuretic peptide variant, the peptide being set forth in SEQ ID NO:5 wherein Xaa=Leu, Ile, Val; Xbb=Lys, Leu, Met; Xcc=Leu, Ile, Ala, Val; Xdd=Ser, Ala, Gly, Thr, Asn; Xee=Met, Ala, Trp, His, Lys, Ser, Gly; Xff=Gly, Lys, Ala, Leu; and Xgg=Leu, Met, and a carrier or excipient, with the proviso that SEQ ID NO:5 is other than amino acid sequence set forth in SEQ ID NO:2. As the Examiner acknowledges, the specification is enabling for a pharmaceutical composition comprising CNP variants according to SEQ ID NO:5. Further, amended claim 31 specifies that SEQ ID NO:5 is other than amino acid sequence set forth in SEQ ID NO:2, and therefore excludes inactive CNP variants, such peptides set forth in SEQ ID NOS: 24-25, 27, 30-31, and 34, as well as SEQ ID NOS: 36, 53, 61, 63-64, and 70-71. Thus, amended claim 31 meets the enablement requirement under 35 U.S.C. § 112 as being fully enabled by the specification.

Likewise, the specification is enabling for amended claim 40, which recites a pharmaceutical composition comprising a natriuretic peptide fused to a carrier protein forming a natriuretic peptide-carrier protein fusion protein, wherein the carrier protein is a bone growth plate-specific protein (see, for example, p. 6, lines 12-23 (describing fusing an NP to a carrier domain to form a fusion protein); p. 23, lines 18-2 (describing selection of a carrier protein)).

Each of dependent claims 32, 36-38, and 42 includes an additional limitation that further defines the claimed composition. Claims 43-44 are cancelled. Therefore, the rejection of claims 31-32, 36-38 and 40-44 for enablement should be withdrawn.

Claim 39 is also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In response, claim 39 is amended to recite that the claimed pharmaceutical composition further comprises an inhibitor of a specific tyrosine kinase, fibroblast growth factor receptor 3 (FGFR3) tyrosine kinase. Support for this amendment is found at, for example, page 6, lines 6-11 of the specification, which provides that overstimulation of FGFR3 results in bone growth inhibition and that the method according to the invention for treating skeletal dysplasias includes administering a pharmaceutical composition comprising an NP and a receptor kinase inhibitor, in particular a tyrosine kinase inhibitor including, but not limited to, those disclosed in US Patent No. 6,329,375 or 6,344,459. Thus, the rejection of claim 39 for enablement should be withdrawn.

Accordingly, all rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Claim Rejections -- 35 U.S.C. § 102(b)

Claims 31-32 and 43-44 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,434,133 to Tanaka et al. ("Tanaka"). Tanaka discloses synthesis of derivatives of CNP, which is SEQ ID NO:2, and a vascular smooth muscle cell growth suppressing agent that contains such peptides as an effective ingredient. SEQ ID NO:2 is specifically excluded from amended claim 31, however. Thus, the rejection of claim 31 as being anticipated by Tanaka should be withdrawn. Claims 32 and 43-44 are cancelled.

Claims 31-33 are rejected under 35 U.S.C. § 102(b) as being anticipated by Suzuki et al. (FEBS 282:321-25 (1991)) ("Suzuki"). Suzuki relates to a high molecular weight variant of CNP isolated from cardiac atria and ventricles of European dogfish. The peptide disclosed in Suzuki consists of 115 amino acids and includes a C-terminal segment having significant homology to mammalian CNP. Suzuki hypothesizes that the 155-amino acid form is a prohormone since the peptide has a consensus cleavage site at amino acid 92-93, but admits that a cleaved, or mature, peptide has not been identified (see p. 323). Thus, Suzuki does not disclose a pharmaceutical composition for bone elongation or treating skeletal dysplasias comprising at least one natriuretic peptide variant as recited in the present claims. Further, even assuming that a mature peptide were identified, the amino acid sequence corresponding to such peptide is excluded from the scope of SEQ ID NO:5 recited in the claims (see p. 324). Accordingly, the rejection over Suzuki should be withdrawn.

Claims 31 and 36-38 are rejected under 35 U.S.C. § 102(b) as being anticipated by H. Ohbayashi et al., "Neutral Endopeptidase 3.4.24.11 Inhibition Potentiates the Inhibitory Effects of Type-C Natriuretic Peptide on Leukotriene D_4-Induced Airway Changes," *Clin. Exp. Pharma. Physiol.*, vol. 25, 986-91 (1998) ("Ohbayashi"), which the Examiner cited as disclosing co-administration of thiorphan with administration of CNP. Since amended claim 31 excludes CNP, the rejection over Ohbayashi should be withdrawn.

Claims 31, 40 and 42 are rejected under 35 U.S.C. § 102(b) as being anticipated by European Patent No. EP 0528686 ("Yabuta"). Yabuta is directed to a process for producing a target peptide by culturing host cells transformed with a plasmid able to express a gene coding for a fusion protein; obtaining an insoluble fraction comprising inculsion bodies by homogenization of the cultured cells of the transformant body; solubilizing of a fusion protein in the inclusion bodies by treatment with solubilizing agent; and cleaving the peptide bond between the C-terminal of the linker amino acid

residue and the N-terminal of the target peptide of the solubilized fusion protein to release the target peptide from the other peptides. The target peptide fusion protein disclosed in Yabuta is a target peptide fused to a protective peptide, which is a fragment of *E. coli* β-galactosidase. Because Yabuta requires the peptide bond be cleaved between the C-terminal of the linker amino acid residue and the N-terminal of the target peptide to release the target peptide, Yabuta in fact teaches away from a composition comprising a fusion protein and does not disclose or suggest a pharmaceutical composition as recited in claims 40 and 42. In contrast to Yabuta, the natriuretic peptide-carrier fusion protein according to the claims is intended to remain a single entity in order to effect targeting of the natriuretic peptide to the growth plate of the bone. In order to expedite prosecution of this application, however, claim 40 is amended to recite that the carrier protein is a bone growth plate-specific protein. Support for this recitation is found at, for example, page 23, lines 18-29 of the specification. Claim 42 depends from claim 40. With respect to claim 31, Yabuta also does not disclose or suggest a pharmaceutical composition as recited in amended claim 31, which specifically excludes CNP. Thus, the rejection of claims 31, 40 and 42 over Yabuta should be withdrawn.

Accordingly, all rejections under 35 U.S.C. § 102(b) should be withdrawn.

Claim Rejections -- 35 U.S.C. § 103(a)

Claims 31, 40 and 41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yabuta, and further in view of Rivera et al. (*Science* 287:826-30 (2000)) ("Rivera") and Mericq et al. (*J. Clin. Endocronol. Metab.* 85:569-73 (2000)) ("Mericq").

As discussed above, however, Yabuta does not disclose or suggest the pharmaceutical compositions as recited in claims 31 and 40, and dependent claim 41, which depends from claim 40 and includes a further limitation that the carrier protein comprises growth hormone. Yabuta, in combination with Rivera and Mericq, also does not disclose or suggest the compositions as recited in claims 31, 40 and 41.

Rivera is directed to a system for direct pharmacologic control of protein secretion where a protein is engineered such that it accumulates as aggregates in the endoplasmic reticulum (ER). Rivera discloses that a therapeutic protein of interest is reversibly retained in the ER by expressing it as a fusion protein that includes a conditional aggregation domain (CAD). Because the CAD moiety must be removed to produce biologically active therapeutic protein, a furin cleavage sequence is imposed between the CAD and the therapeutic protein such that the therapeutic protein is released

and secreted. Thus, Rivera, like Yabuta, teaches cleaving the peptide bond to release a therapeutic protein, but does not disclose or suggest a pharmaceutical composition comprising a natriuretic peptide fused to a carrier protein as recited in claim 40.

Mericq merely relates to effects of growth hormone (GH) therapies in the treatment of adolescents with GH deficiency, where administration of GH with LHRH-A is compared with administration of GH alone. Thus, Mericq does not disclose or suggest the pharmaceutical compositions as recited in the claims, alone or in combination with the other references.

None of the cited references, alone or in combination, discloses a pharmaceutical composition as recited in claim 31 or a pharmaceutical composition comprising a natriuretic peptide fused to a carrier protein forming a natriuretic peptide-carrier protein fusion protein as recited in claim 40 or 41. Therefore, the rejection of claims 31, 40 and 41 under 35 U.S.C. § 103(a) should be withdrawn.

Finally, Applicants respectfully submit that withdrawn claims 45-59 and 67-96 depend directly or indirectly from claim 31. Accordingly, these claims should be re-joined and allowed when claim 31 is allowed.

In view of the above, the entire application is believed to be in condition for allowance, early notification of such would be appreciated. Should the Examiner not agree, a personal or telephonic interview is respectfully requested to discuss any remaining issues in order to expedite the eventual allowance of the claims.

Respectfully submitted,

5-23-06
Date

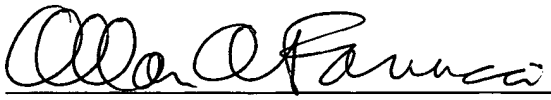

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Figure 3A

CNP 1-22 SEQ ID NO:1 deleted

G L S K G C F G L K L D R I G S M S G L G C

Figure 3B

CNP 5-22 SEQ ID NO:2 deleted

C F G L K L D R I G S M S G L G C

Figure 3C

Human ANP: SEQ ID NO:3 S L R R S S C F G G R M D R I G A Q S G L G C N S F R Y

Human BNP-32: SEQ ID NO:4 S P K M V Q G S G C F G R K M D R I S S S S G L G C K V L R R H

Human CNP 1-22: SEQ ID NO:1 G L S K G C F G L K L D R I G S M S G L G C

SEQ ID NO:5 deleted

Cys-Phe-Gly-Xaa-Xbb-Xcc-**Asp-Arg-Ile-Gly**-Xdd-Xee-**Ser**-Xff-Xgg-**Gly-Cys**

Xaa=**Leu, Ile, Val**; Xbb=**Lys, Leu, Met**; Xcc=**Leu, Ile, Ala, Val**;

Xdd=**Ser, Ala, Gly, Thr, Asn**; Xee=**Met, Ala, Lys, Trp**; Xff=**Gly, Lys, Ala, Leu**; Xgg=**Leu, Met**